Section II (Remarks)

Rejections and Traversal Thereof

In the October 20, 2008 Office Action, claims 1-17 were rejected on reference grounds, including:

- a rejection of claims 12-17 under 35 U.S.C. 102(b) as being anticipated by Grandfils et al. (US 5,962,566); and
- a rejection of claims 1-17 under 35 U.S.C. 103(a) as being unpatentable over Grandfils (US 5,962,566) in view of Levy et al. (WO 96/20698).

Such rejection of claims is traversed, and reconsideration of the patentability of the pending claims 1-17 is requested on the basis of the following remarks.

Empirical Evidence – Preparation of Nanoparticles With and Without Cholesterol Using the Process Disclosed in Grandfils Reference

Applicants have developed the following empirical evidence that is probative of the patentability of their claimed invention.

This evidence can be supplementally furnished in a Declaration under 37 CFR 1.132 if desired by the examiner to complete the record.

In this empirical effort, microparticles were prepared without cholesterol (Example A) using the process disclosed in Grandfils, and by a corresponding process except with cholesterol (Example B). The procedure and results are set out below.

Example A - Preparation of Microparticles from a Blend and Without Cholesterol

Initially, a blend of polymers was prepared by dissolution of PLGA 503 (22.5 mg) and Poloxamer (22.56 mg) in dichloromethane, at room temperature. Afterwards, this solution was heated at 40ºC and the solvent was removed until a dried blend was obtained. This blend was

subsequently dissolved in DMSO (vortex stirring), and the solution obtained was added to an aqueous phase (70 mL of mQH_2O) with vigorous stirring using turrax for 2 minutes followed by stirring in a magnetic stirrer. After the formulation was prepared, particles were formed (as well as some visible aggregates) with a mean particle size of **5.8±1 µm.**

Example B - Preparation of Nanoparticles from a Blend and With Cholesterol

Initially, a blend of polymers is prepared by dissolution of PLGA 503 (22.5 mg) and Poloxamer (22.56 mg) in dichloromethane, at room temperature. Afterwards, this solution was heated at 40ºC and the solvent was removed until a dried blend was obtained. Cholesterol (2.75 mg) was dissolved in DMSO and then was added to the blend and dissolved at room temperature. This solution of polymers and cholesterol was added to the aqueous phase (70 mL of mQH_2O) with vigorous stirring using turrax for 2 minutes followed by stirring in a magnetic stirrer. After the formulation was prepared, nanoparticles were obtained with a mean particle size of **119±17 nm** and a Zeta potential of -25±3 mV.

These results demonstrate that the process of Grandfils, using a polar solvent (DMSO) and without cholesterol, produces a mean particle size in the micron range (5.8 ± 1 µm), instead of the nano range (50-200 nm) of the present invention.

The Rejection of Claims 12-17 Under §102 Based on Grandfils

The rejection of claims 12-17 has been maintained on the basis that the applicant has not shown that the nanoparticles obtained by the method of the invention differ from those of Grandfils.

The foregoing empirical results, however, demonstrate that the process of Grandfils using a polar solvent (DMSO) without cholesterol provides a mean particle size in the micron range (5.8±1 µm), instead of the nano range (50-200 nm) of the particles of the present invention.

As mentioned above, the evidence demonstrates that the process of Grandfils necessarily requires the addition of cholesterol and the polar solvent in order to obtain nanoparticles.

In column 4, lines 18-21, Grandfils states that the solvent (polar solvent) is removed, but not completely ("up to 99.9%"). Thus, the nanoparticles of Grandfils necessarily contain polar organic solvent (i.e., DMSO) as an impurity.

This is not the case for the nanoparticles recited in claim 12, since they have been formed by a process involving a non-polar product.

Accordingly, the nanoparticles of claim 12, and of claims 13-17 depending from claim 12, are different from the nanoparticles of Grandfils.

It is correspondingly requested that the rejection of claims 12-17 be withdrawn.

Rejection of Claims 1-17 Under §103 Based on Grandfils in View of Levy

Claims 1-17 have been rejected as obvious over Grandfils in view of Levy (WO 96/20698). The rejection is based on the assertion that the present invention differs from Grandfils in that the process comprises dissolving the polymer in a non-polar organic solvent which is then mixed directly with a polar phase, and in that it uses polyanhydrides or poloxamines.

Levy has been cited as disclosing an organic phase formed by the polymer, the active ingredient and a non-polar solvent (e.g. methylene chloride), which then is added directly to the aqueous phase. The Office Action specifically draws attention to Example 1 of Levy. According to the Office Action, this would have lead the skilled person into modifying the process disclosed in Grandfils by applying the same procedure as taught in Levy so as to provide a more simple method for the preparation of nanoparticles.

In response, it is pointed out that the Office Action does not properly substantiate why the skilled person would combine the teachings. Grandfils is directed to a process for the preparation of nanoparticles which comprise a low molecular lipophilic compound and/or a polypeptide as a drug. The Office Action contends that the skilled person would have combined the teachings of Grandfils with Levy. At page 5 the Office Action states "When hydrophilic active agents [emphasis added] are to be incorporated into the nanoparticles…". Thus, Grandfils and Levy are directed to nanoparticles comprising active ingredients of a different nature. There is no logical basis for the implicit assumption that the skilled person would have combined the teachings of Grandfils and Levy.

Additionally, the Office Action fails to notice that the aqueous phase in Example 1 of Levy is a 2% w/v aqueous PVA solution, PVA being a surfactant. Use of this PVA solution requires two previous steps (see page 31, lines 4-11 of Levy):

- saturation with methylene chloride because "methylene chloride, which is partially soluble in water, would cause the polymer to separate from the drug/polymer solution immediately upon its addition into the aqueous phase because of diffusion of methylene chloride into water;" and
- filtration of the PVA solution in order to remove high molecular weight water insoluble PVA.

The need of additional previous steps in Levy would certainly not appeal to a skilled person in search of a simpler method for the production of nanoparticles. In fact, Levy would discourage the skilled person, who would be lead to believe that additional previous steps are required.

According to the Office Action, "One of ordinary skill in the art particularly in view of the teachings of Levy et al. would be aware that the polymers dissolved in a non-polar organic solvent need not be evaporated and resuspended in a polar organic solvent in order for nanoparticles to be produced when the organic solution is mixed with the polar phase".

This conclusion, however, ignores the fact that the Levy teaches additional previous steps which would deter one skilled in the art in the search of a simpler procedure.

Such conclusion also ignores the fact that in contrast with Levy or Grandfils, the instant invention does not require surfactants such as PVA or cholesterol. Levy does not in any way teach or suggest how the procedure in Grandfils could be improved in order to arrive to the present invention.

Accordingly, the method of claim 1, and dependent claims 2-11 thereunder, and the nanoparticles that are the product of such process, as claimed in claim 12 and claims 13-17 dependent thereunder, find no derivative basis in the combination of Grandfils in view of Levy.

It therefore is requested that the rejection of claims 1-17 over Grandfils in view of Levy be withdrawn.

CONCLUSION

Based on the foregoing, all of Applicants' pending claims 1-17 are patentably distinguished over the art, and in form and condition for allowance. The examiner is requested to favorably consider the foregoing, and to responsively issue a Notice of Allowance. If any issues require further resolution, the examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss same.

Respectfully submitted,

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